# Ototoxic Drugs, Chemicals and Heavy Metals in the Workplace

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http://www.workplaceintegra.com/hearing-articles/Ototoxics-in-Workplace.htm

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## Occurrence

An estimated 15,000 to 160,000 drugs, chemicals and/or heavy metals may be toxic to the senses. Ototoxic substances are estimated to be between 5,200 and 56,000 agents. Possibly 75% of the ototoxic drugs have a low occurrence ototoxic effect of 1 or 2 per 1,000. Another 22% have a moderate ototoxic effect and that approximately 3% have a high occurrence of 20% (200 per 1,000).

## Physiology

When discussing the effects of drugs and/or chemicals, it is important to understand some physiological relationships. One ancient axiom states, “The ear is connected to the entire body”. This is true not only for our alertive reactions but is also true for the kidneys, balance, and eyes. Balance and hearing are so connected that it is stated by some that the primary function of the ear is balance, because balance is the more primordial function. The balance and hearing mechanisms are serviced by the same blood supply, cranial nerve and share the same fluid. Most often the effects of ototoxic drugs and chemicals will affect balance before hearing. The relationship of the kidneys to the ear is established in the kidney’s elimination of harmful excesses in the blood. Weak, damaged or reduced functioning by loop diuretics will result in less filtering and a build up of chemical concentrations in the blood stream. This combined with the ability of some chemicals to target fluid in the balance/auditory mechanism will result in additional risk and/or impairment.

## Risk Factors

**(Ototoxic Drugs Exposed, Bauman, Neil G., 2003)**

- *Youth* – The very young, including the unborn child (6 to 8 weeks) are susceptible to permanent deafness and/or balance problems.
- *Age* – Most hearing loss from age will occur beyond age 60 and the hearing loss from ototoxicity is an addition.

- *Genetics* – Particularly with mycin drugs.
- *Existing hearing and balance problems* – Persons with problems are more likely to have additional problems as shown with some chemotherapy drugs as Cisplatin.
- *Extreme sensitivity* to a drug or chemical
- *Repeated continuous exposure* or exposure for a long duration
- *Improper dosage* or administration
- *Dehydration* – Ototoxicity is a threat particularly with loop diuretics increasing the concentration in the blood.
- *Two or more ototoxic drugs or chemicals.* Loop diuretics and aminoglycosides (mycin) drug combinations are particularly ototoxic. Even order of taking drugs can effect severity of ototoxicity.
- *Poor general health*, abnormal blood laboratory values, or bacteremia.
- *Radiation treatments* on the head or ear.
- *Eye or proprioceptive* (balance) can predispose more serious problems.
- *Grapefruit juice* can increase 10 to 250 times the amount of drug absorbed into the blood stream.

# Main Ototoxic Drug Classes

**(Ototoxic Drugs Exposed, Bauman, Neil G., 2003)**

- Aminoglycoside as antibiotics (Gentamicin, Kenomycin, Neomycin)
- Salicylates as aspirin
- Quinines
- Loop diuretics
- Anti-neoplastics as anti-cancer drugs (Cisplantin)
- Others, non-steroidal anti-inflammatory, antibiotics, antihistamines, cardiovascular, anti-convulsant, anti-depressant and anti-psychotic drugs.

# Characteristics of Drug and Chemical Ototoxicity

**Synergistic Effects**

Noise and drugs (chemicals) have been shown to be synergistic in their damaging effects to the balance/hearing mechanisms. Synergistic damage is multiples of the expected damage of either agent alone.

| | |
|---|---|
| Noise Alone | 4.1 risk factor |
| Solvent Mixture Alone | 5.0 risk factor |
| Noise and Toluene | 10 to 27.5 risk factor |

**High Frequency Hearing Loss**

Many chemicals and most drugs will affect the higher frequencies first. The recognized range of human hearing is 20 to 20,000Hz. Current industrial and clinical hearing testing includes the frequencies ranging from 125 Hz to 8,000Hz. The initial hearing loss may well be in frequencies above 8,000Hz.

It is possible to monitor hearing loss caused by drugs and chemicals. This is usually done with children undergoing chemotherapy treatment. Pre, during, and post hearing testing of the extreme high frequencies to monitor the highest five-frequencies the patient can respond to, provides a clinical procedure to identify changes caused by drugs and chemicals. These frequencies are above the standard 500Hz to 8,000Hz testing done in industry. They include 1/6 octaves above 8,000Hz up to 20,000Hz.

**Prolonged Susceptibility**

After exposure to chemicals (drugs) the period of time the ear may be synergistically susceptible to increased damage may be for periods as long as one year (Cisplantin).

**Side Effects (Ototoxic Drugs Exposed, Bauman, Neil G., 2003)**

Drugs and chemicals include the following most frequent side effects in order of most common occurrence:

- Dizziness
- Tinnitus
- Vertigo
- Ataxia
- Hearing Loss

To a lesser degree, side effects can include everything from otitis media, to hyperacusis to auditory hallucinations.

**Auditory Processing**

At least one-third of the population has some form of auditory processing (AP) problem. Some are born with AP, others missed auditory stimulation at the critical maturational period (chronic childhood otitis media), still others have AP as a result of aging as well as drugs and chemicals. The inability to understand what has been heard is a common complaint of those with processing problems. Because drugs and chemicals can be neurotoxins, the damage can be generalized in scope including the cortex, brain stem, and/or cranial nerves. Even though the first observable symptoms may be balance or hearing, the subtle associations of language and conceptualization will suffer significantly.

**Pure Tone Audiometric Configuration**

It is not possible to diagnose the cause of hearing loss from the pure tone air conduction configurations. Every configuration can be mimicked by other pathologies. Combinations of

factors, as a 55 year old who has been in noise for 30 years, shoots guns, has a history of hospitalization for a respiratory infection treated with mycin drugs and currently takes medication for hypertension, compound the impression. However, some broad generalities can be made when discussing threshold configurations if it is understood that everything can look like something else, and often does.

Drugs many times will affect the higher frequencies beginning with frequencies above 8K Hz. Therefore the configuration is sloping with the higher the frequency the greater the loss.

Heavy metals usually target an organ or structure, therefore the configuration is characteristic to the area of damage. Lead causes a demyelination of VIIIcn with a downward sloping audiogram leaving the cochlea intact, however, arsenic targets the apex of the cochlea showing a low frequency sensory-neural hearing loss.

Organic solvents can look like anything, including noise without noise exposure, effect either one-or-both ears, are dose/time dependent but do not necessarily effect everyone.

# Chemicals

## *Gas*

### Carbon Monoxide

In low-dose, oxygen deprivation can result in mild threshold shifts in all frequencies usually temporary.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 20 | 20 | 20 | 20 | 20 | 20 | 20 |

In high-dose, carbon monoxide there are histological changes in the Organ of Corti resulting in oxidative metabolism of the inner ear. Carbon monoxide is synergistic with noise resulting in large threshold shifts at all frequencies.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 30 | 35 | 40 | 45 | 50 | 45 | 40 |

## *Heavy Metals*

The effects of heavy metals on hearing have been known for several centuries. Members of the hatter's trade, using mercury nitrate in manufacturing felting hats, were referred to as, "Mad as a hatter."

**Lead (pb)**

This metal causes a demyelination of VIIIcn leaving the cochlea unharmed. All frequencies show loss with a greater loss in the high frequencies. Vertigo is often a symptom. It has also been noted that the longer exposure to lead the greater the severity of the hearing loss.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 30 | 35 | 40 | 45 | 40 | 60 | 70 |

**Arsenic (As)**

Most commonly found in the manufacturing of parasite and micro organism inhibitors. Arsenic over exposure results in disorders in the Organ of Corti beginning at the apex. Hearing losses are greater in the lower frequencies at 125, 250, and 500 Hz. Balance problems are also noted.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 45 | 30 | 10 | 05 | 10 | 15 | 15 |

**Mercury (Hg)**

Mercury is found in solder, the manufacturing of thermometers and detonators. Injury occurs in the early and middle stages in the cochlea with sensory cell destruction. In later stages the injury is retro cochlear as well. Hyperadditive with noise, the loss is commonly bilateral with auditory processing difficulties. Hearing loss is in the entire range with greater losses in the high frequencies. However, loss does not always occur even with severe neurological symptoms. Hearing loss reportedly occurs 80% of the time.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 25 | 30 | 35 | 40 | 45 | 50 | 55 |

**Manganese (Mn)**

Found in battery manufacturing, electroplating, and the processing of ferrous metals the auditory site of lesion is unknown. However, manganese results in a loss in both the low and high frequencies with the mid range showing better hearing.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 40 | 20 | 25 | 40 | 45 | 50 | 55 |

**Organotins; Trimethyltin (TMT), Tridthyltin (TET)**

Organotins are used as heat stabilizers for polyvinyl chloride in piping, siding and window casings. Also used as catalysts for polyurethane foam, marine paint, wood preservative, fungicides and in the poultry industry.

TMT hearing losses are possibly reversible and can cause cochlear lesions.

TET results in decreased myelin content in CNS and white matter edema with a rapid onset.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 25 | 30 | 35 | 30 | 35 | 35 | 40 |

## *Organic Solvents*

In the early stages oto-neurologic disturbances may include vertigo and nausea. Histopathologic studies have shown damage in the sensory cells of the inner ear. In later stages, chronic toxic encephalopathy occurs. The syndrome develops slowly with no pathological findings present in the first years. Later, psychometric, auditory, oto-neurologic testing will show disturbances. The site of lesion is within the cerebellum and brainstem regions. Auditory processing balance and Auditory Brainstem Response (ABR) testing may show disturbances. Even though effects are time and dose dependent, not everyone is affected. Important initial complaints are headaches, nausea, balance problems as dizziness, memory loss, fatigue and hearing difficulties.

**Carbon disulfide**

Used in solvents and insecticide, the auditory site of lesion is most often retro cochlear. In noise levels of 86 to 89 dBA, the incidence of hearing loss was 47 % within two years. With three years of exposure the incidence rose to 71%. Common dysfunctions include abnormal acoustic reflex and central vestibular disorders.

A typical audiogram for carbon disulfide exposure shows losses in the high frequencies, however, a large number of subjects show additional loss in the lower frequencies regardless of age.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 30 | 35 | 45 | 55 | 70 | 75 | NR |

**Trichloroethylene**

This solvent is used as a degreaser, dry cleaning agent, spot remover and rug cleaner. It is used in the production of paints, waxes, pesticides, adhesives and lubricants. Destruction of sensory cells of the inner ear is suspected. It results in a bilateral symmetrical high frequency dip beginning at 2K or 3K Hz and is associated with balance problems.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 20 | 20 | 40 | 60 | 65 | 65 | 50 |

**Styrene**

Styrene is used in the production of plastics, synthetic rubber, resins and insulating materials. Exposure results in sensory cell damage with abnormal acoustic reflex and abnormal ABR. Often distorted speech test results are reported.

Lower concentrations of styrene show losses above 8K Hz and do not indicate loss other than noise.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 10 | 10 | 10 | 30 | 50 | 45 | 30 |

Higher concentrations (1200 ppm) have losses at all frequencies.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 25 | 30 | 40 | 60 | 65 | 70 | 65 |

**Xylene**

Known as the most prevalent, exposing more people, and the most toxic of all the organic solvents, xylene is found in paints, varnishes, and thinners. It produces damage in the sensory cells of the inner ear. No configurations were found discussed in the literature

**Toluene**

2.6 million metric tons are produced annually via air pollution and auto emissions.

Toluene is the most studied organic solvent. It is used in the manufacturing of chemicals, paints, lacquers, adhesives, rubber, rotogravure printing, leather tanning, spray painting, glue, etc. It produces cochlear damage.

The synergistic effects can result in an increased risk 27.5 times. Balance problems and abnormal acoustic reflexes are significant symptoms. The audiogram configuration can be flat, bilateral or unilateral; however the most common configuration is a dip at 3K to 6K Hz (as noise) even in the absence of noise.

Example Audiogram taken from literature.

| .5K | 1K | 2K | 3K | 4K | 6K | 8K |
|---|---|---|---|---|---|---|
| 20 | 20 | 30 | 40 | 45 | 60 | 40 |

# Issues Concerning Ototoxic Drugs and Chemicals in the Workplace

- The possible early detection of neurotoxic damage by closer monitoring of balance and hearing is needed. Hopefully, detection would be at a stage early enough for effects to be reversible.
- The synergistic effects of chemicals, drugs and noise need to be recognized by the medical, safety and industrial hygiene communities. There is documented evidence that when chemicals, drugs and noise are administered simultaneously, the biological results are not necessarily predicted on the knowledge of each alone. Safe levels of either agent can synergistically result in significant balance and auditory injury. It is an established fact that noise acts synergistically with certain drugs and chemicals.
- Adequacy of pure tone testing as an indicator of occupational hearing loss or as a tool useful in the early detection of neuron-toxic effects is questionable. With chemicals capable of causing retro cochlear damage resulting in balance problems, difficulty understanding interrupted speech and speech in noise, absence of recruitment and abnormal acoustic reflexes, the idea of testing hearing using a single vibration source stimulating specific and limited areas of the cochlea seem paltry, indeed.

- The adequacy of existing regulations which identify noise as the sole agent in initiating and conducting an occupational hearing conservation program seem limited in scope and purpose. Evidence suggests that both the individual and possible synergistic affects of drugs and chemicals will dictate a broader definition of occupational hearing conservation.

- The medical and audiological professions must develop evaluation protocols to differentially diagnose the effects of drugs, chemicals and noise. As with all clinical evaluations, rarely do all the test results point in a single direction, but when a preponderance of data indicates a direction and/or site of lesion, a diagnosis is made.

Drugs and chemicals can effect auditory brainstem response results, demonstrate balance and equilibrium problems, result in abnormal acoustic reflexes, demonstrate hearing loss initially above 8K Hz, often do not show recruitment and are capable of demonstrating measurable auditory processing difficulties to staggered word tests. Tinnitus is often present and may disappear or be reduced when medication or exposure ceases.

Noise induced hearing loss results primarily in cochlear dysfunction, does not show abnormal auditory brainstem responses, does not usually effect balance, demonstrates recruitment, shows the presence of acoustic reflexes within measurable threshold ranges, shows a dip in hearing at 3, 4, and/or 6 K Hz in the initial stages, does have recruitment and most often results in speech discrimination problems not necessarily auditory processing difficulties. Tinnitus may not be reported in noise induced (continuous exposure to high levels of noise) but a ringing is associated with blast wave exposure (as gunfire). Noise is not associated with a roaring, buzzing or pulsating tinnitus.

**References and Materials for Further Reading**


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# Ototoxicity


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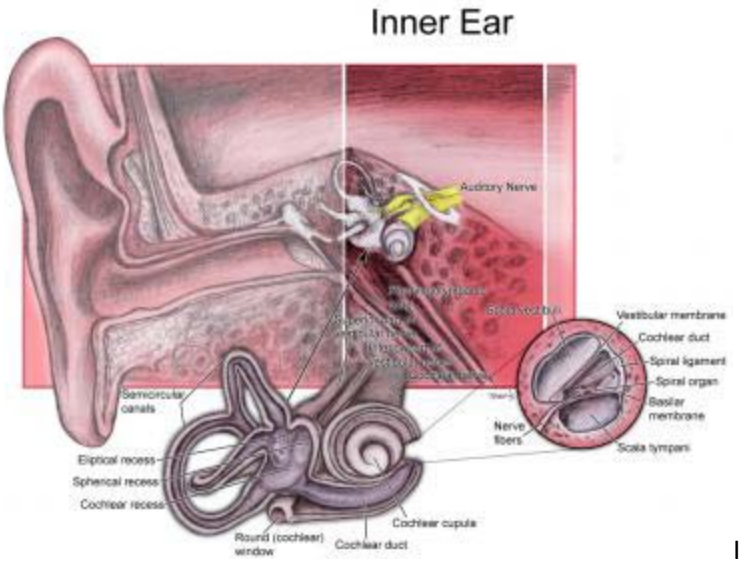
## Overview

Any drug with the potential to cause toxic reactions to structures of the inner ear, including the cochlea, vestibule, semicircular canals, and otoliths, is considered ototoxic. Drug-induced damage to these structures of the auditory and balance system can result in hearing loss, tinnitus, and dysequilibrium or dizziness. The propensity of specific classes of drugs to cause ototoxicity has been well established, and over 100 classes of drugs have been associated with ototoxicity.

Ototoxicity came to the forefront of clinical attention with the discovery of streptomycin in 1944. Streptomycin was used successfully in the treatment of tuberculosis; however, a substantial number of treated patients were found to develop irreversible cochlear and vestibular dysfunction. [1] These findings, coupled with ototoxicity associated with later development of other aminoglycosides, led to a great deal of clinical and basic scientific research into the etiology and mechanisms of ototoxicity. Today, many well-known pharmacologic agents have been shown to have toxic effects to the cochleovestibular system. The list includes aminoglycosides and other antibiotics, platinum-based antineoplastic agents, salicylates, quinine, and loop diuretics.

An image depicting inner ear anatomy can be seen below.




Inner ear anatomy.

Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus. Hearing loss can be temporary but is usually irreversible with most agents. Generally, antibiotic-induced ototoxicity is bilaterally symmetrical, but it can be asymmetrical. The usual time of onset is often unpredictable, and marked hearing loss can occur even after a single dose. Additionally, hearing loss may not manifest until several weeks or months after completion of antibiotic or antineoplastic therapy.

Vestibular injury is also a notable adverse effect of aminoglycoside antibiotics and may appear early on with positional nystagmus. If severe, vestibular toxicity can lead to dysequilibrium and oscillopsia.

Permanent hearing loss or balance disorders caused by ototoxic drugs may have serious communication, educational, and social consequences. Therefore, the benefits of ototoxic drugs must be weighed against the potential risks, and alternative medications should be considered when appropriate. Management emphasis is on prevention, as most hearing loss is irreversible. No therapy is currently available to reverse ototoxic damage; however, basic scientists and clinicians are continually seeking to find new methods to minimize ototoxic injury while retaining the therapeutic efficacy of these agents. For severe hearing loss, amplification may be the only treatment option.

For patient education resources, see the Ear, Nose, and Throat Center, as well as Hearing Loss.